

COVER PAGE STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN:

OFFICIAL TITLE:

Effects of ultrasound-guided bilateral suprazygomatic maxillary nerve block on postoperative pain after elective bimaxillary osteotomy in adult patients.

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SUMMARY

Bimaxillary osteotomy is a surgery procedure of the orthognathic surgery field with the aim to correct dental and facial abnormalities, for both functional and aesthetic cases. The incidence of this abnormality is 5-10% of the population, and its etiology is unknown, with genetic, environmental and embryonic factors related. The surgical technique is complex, and requires osteotomy of the maxillary and jaw, which allows toward, forward, impact and rotation of these bones to fix the edges of the face. The anesthetic management of these patients is a challenge because of the difficult airway management and the perioperative pain control. Multimodal approach for pain control is a fact, and the use of local and regional anesthesia is mandatory. We propose bilateral suprazigomatic maxillary nerve block for a proper control of postoperative pain after bimaxillary osteotomy.

INTRODUCTION

Bimaxillary osteotomy is a surgical procedure in the field of orthognathic surgery (from Latin, "orthos" straight and "gnathos" jaw) for the correction of dentofacial deformities, both for functional and aesthetic reasons. The incidence of this deformity is estimated to be around the 5-10% of the population. Genetic, environmental and embryonic factors are postulated to be the origin of such deformity, though its origin is still unknown. The surgical technique is complex, with the performance of mandibular and upper jaw osteotomies that allow to advance, retrude, impact and rotate these bones, to align the facial axes. For all these reasons, the anesthetic management of these patients is a challenge. First, the foreseeable difficulty of managing the patient's airway; and second, the control of the patient's pain in the perioperative period. Therefore, bimaxillary osteotomy is a frequent surgery and potentially painful in adults. Bimaxillary surgery under general anesthesia is the common practice. And peripheral non-ultrasound-guided peripheral nerve blocks are widely used by surgeons. These minor blockades are used to avoid the undesired effects of anesthetics and analgesics; mainly the adverse respiratory effects of opioids. The practice of loco-regional anesthesia provides a control of perioperative pain in a multimodal way showing effective postoperative analgesia and minimizing the respiratory depression caused by the excess use of opioids.

In general, during bimaxillary surgery the surgeon performs the infiltrations with local anesthetic (LA) in a pre-incisional manner for the blockade of the terminal branches of the maxillary nerve intraorally and intranasally. The choice of LA is influenced by considerations such as the start of action, duration and toxicity. A wide range of LA has been used in maxillofacial surgery, such as lidocaine and ropivacaine among others. Both LA produce a reversible blockade of the sodium channel of the neuronal membrane, and are synthetic derivatives of cocaine. Both possess three essential functional units (hydrophilic tertiary amide chain, linked by an intermediate amide chain, to another lipophilic aromatic ring-portion). This means, both LA are amide type; but even if they belong to the same group of LAs there is still great differences in the beginning of action, duration of action and toxicity. Lidocaine has a faster start of action (short latency) than ropivacaine, and has an antiarrhythmic effect. Ropivacaine is more potent, the action last longer than lidocaine, and is less cardiotoxic than other equipotent LA such as bupivacaine and levobupivacaine.

Subsequently, the introduction of loco-regional nerve blocks has meant for the anesthesiologist, in the last three decades, a revolution in the management and control of perioperative pain. The expansion of the practice of loco-regional nerve blocks has been seen in both upper and lower limbs, as well as in trunk and abdomen. On the contrary, the facial blockages (both superficial and deep) have not experienced the same; laying its practice to the surgeon, or to anesthesiologists working on the chronic pain domain. The subsequent introduction of ultrasonography (USG) in the

1990s in the perioperative period also represented an important advance for anesthesiologist both in terms of safety and in terms of ease of management of venous and arterial catheterizations, and practice of loco-regional blockages. Consequently, USG experienced anesthesiologists have recently published in regards to the use of ultrasounds (US) for the blockage of facial nerves in children and adults undergoing maxillofacial surgery. USG devices are increasingly accessible, more portable, cheaper and safer; and therefore, its introduction in the field of perioperative pain management of maxillofacial surgery has still a long way to go.

The maxillary nerve, just like the ophthalmic, is only sensitive. It is detached from the anterolateral border of the trigeminal ganglion, laterally to the ophthalmic. From its origin, it goes above, crosses the round hole and penetrates into the background of the infratemporal fossa until it enters the pterygopalatine fossa (except the middle meningeal nerve, all its branches reach the pterygopalatine fossa before reaching the facies). In the pterygopalatine fossa the maxillary nerve is located in the upper part of the cavity and passes superiorly to the maxillary artery and superolaterally to the pterygopalatine ganglion. The maxillary nerve receives and conducts the sensitivity of the skin of the cheek, the lower eyelid, the wing of the nose and the upper lip. Its deep branches drive the sensitivity of the mucosa of the lower part of the nasal cavities or respiratory area, and of the dental roots and the gums of the maxilla.

Therefore, in order to produce an effective anesthesia of the maxillary area, the needle can be introduced through the pterygomaxillary fissure to the pterygopalatine fossa, with risk of vascular and nerve puncture. However, with real-time vision of the ultrasound-guided block, these risks will be limited, allowing a direct localization of the maxillary artery, position of the needle and the distribution of LA within the pterygopalatine fossa. The pterygopalatine fossa is anatomically deep and surrounded by bones. The most optimal ultrasound window is the infrazigomatic path, allowing the visualization of the entire axis of the pterygopalatine fossa up to the foramen rotundum.

The usual practice for the ultrasound-guided maxillary nerve block is the placement of the ultrasound probe in an infrazigomatic position and the introduction of the needle by suprazigomatic route for better visualization of the procedure. The approach by suprazigomatic route from the frontozigomatic angle is one of the safest and recommended routes to reach the foramen rotundum. This trajectory limits the insertion of the needle in the anterior portion of the foramen rotundum, avoiding, this way, the inadvertent puncture of the intraorbital content through the infraorbital fissure.

Experienced anesthesiologists in anesthesia for maxillofacial surgery, perform bilateral ultrasound-guided blockade of the maxillary nerve by suprazigomatic route with ropivacaine for greater control of perioperative pain. They avoid the use of a combination of LA for maxillary nerve block. The combination of several local anesthetics in the same nerve block is sometimes used in perioperative anesthesia with the intention of compensating the short duration of action of some agents whose start of action is fast, such as lidocaine, and the high latency of the agents that present a more lasting action, such as ropivacaine. The combination of lidocaine and ropivacaine offers clinical advantages (rapid onset, long duration). However, to date, indications for combining LA are scarce because of the use of catheters in many forms of regional anesthesia that allow to prolong the duration of the block. This is nevertheless not an extended practice among anesthesiologists in maxillofacial surgery. On the other hand, it is important to also remember avoiding the use of maximum doses of two LA combined, which is based on the erroneous belief that their toxicities are independent; on the contrary, the toxicities have an additive character.

Multiple drugs have been used to increase the time of action of LA, such as adrenaline, clonidine, dexamethasone, ketamine and dexmedetomidine, among others. In our patients, adrenaline is always administered along with physiological serum by the surgeon at the local level to improve the surgical field, both in patients who undergo pre-incision infiltration and bilateral blockade of the maxillary nerve. The use of Clonidine is ruled out because it is not supplied in the hospital center where we will carry out the study. The use of dexamethasone and ketamine is ruled out, because they will be administered intravenously in the patient's perioperative period as anti-inflammatory agents and anesthetic adjuvant, respectively. And the use of Dexmedetomidine is also ruled out in order to prolong the effect of the nerve blockade as this indication is not in the technical file.

HYPOTHESIS

Hypothesis tests:

- H0: Patients who receive bilateral ultrasound-guided blockade of the maxillary nerve by suprazigomatic route with ropivacaine and dexmedetomidine don't have less immediate postoperative pain and don't require fewer opioids in the immediate postoperative period than patients who receive a pre-incisional infiltration with lidocaine
- H1: Patients who receive bilateral ultrasound-guided blockade of the maxillary nerve by suprazigomatic route with ropivacaine and dexmedetomidine have less immediate postoperative pain and require fewer opioids in the immediate postoperative period than patients who receive a pre-incisional infiltration with lidocaine

OBJECTIVES

Main objective of the study is the evaluation of the effectiveness of the bilateral ultrasound-guided ultrasound blockade with ropivacaine suprazigomática, compared to the peripheral infiltration of the nerve with lidocaine and adrenaline, on the consumption of opioids for control of perioperative pain of patients intervened of elective bimaxillary osteotomy, evaluated by means of the analogical visual scale of pain in the immediate postoperative period (2 hours postoperatively). The secondary objectives of the study are: comparison of the use of opioids in the intraoperative period (Target Controlled Infusion - TCI ng / ml - intravenous remifentanyl), comparison of the use of rescue opioids (milligrams of intravenous methadone) in the postoperative period in hospitalization (2-18h postoperative), the comparison of the incidence of immediate postoperative nausea and vomiting (PONV) in resuscitation and up to 18 hours after surgery, the comparison of initiation of oral tolerance after the end of surgery, and the registry of complications derived from ultrasound-guided maxillary nerve block.

MATERIAL AND METHODS

Study design

We propose a double-blinded prospective comparative experimental study (patient and nurse). After the approval of the ethics committee of our hospital and the signed consent from each of the patients in the study, patients will be scheduled for bimaxillary osteotomy and will be randomly and prospectively assigned to one of the two groups with a plan to register up to 58 patients. Patients will not know the group that they have been assigned consecutively; and both the postoperative resuscitation nurses and the hospitalization nurses who will perform VAS records, opioid consumption, oral tolerance initiation, PONV and postoperative complications, will also be unaware of the analgesic treatment that the patient has received in the operating room. Patients will be assigned randomly to one group or another:

- Control group: patients undergoing elective bimaxillary osteotomy who receive a preincisional infiltration of lidocaine and adrenaline.
- Study group: patients undergoing elective bimaxillary osteotomy with bilateral echoguided blockade of the maxillary nerve by suprazigomatic route with ropivacaine; and infiltration with preincisional adrenaline.

Population

The source and mechanism of subject selection is a convenience sample, with consecutive recruitment in our clinic at the Maxillofacial Institute of Teknon Medical Center.

The criteria for the selection of subjects is the following. The inclusion criteria are patients who undergo scheduled bimaxillary surgery. The exclusion criteria are: the refusal to participate in the study, patients who are scheduled for bimaxillary surgery together with another complementary surgical procedure (such as mentoplasty, rhinoplasty, blepharoplasty), age <18 years, reinterventions, urgent surgeries, allergies to local anesthetics, allergies to anti-inflammatories agents, allergies to opioids, ASA ≥3.

Procedure / Intervention

Patients will be received in the surgical area and a venous access line will be placed where premedication (Midazolam 2mg / ev) and antibiotic prophylaxis (amoxicillin-clavulamic 2g / ev or Clindamycin 600mg / ev in case of patients allergic to beta-lactams) will be administered. They will be monitored in the operating room (SpO₂, electrocardiogram, non-invasive blood pressure – NIBP-, Bispectral index, Train of four TOF - CUFF neuromuscular monitor) and general intravenous anesthesia will be carried out (anesthetic induction: fentanyl 2mcg / kg / ev, propofol 2mg / kg / ev, rocuronium 0.6mg / kg / ev; and anesthetic maintenance: sevoflurane CAM 1.2 and remifentanyl TCI - Effective Concentration 2ng / ml). After the nasal intubation of the patient, the administration of the LA will proceed by the following routes:

- Control Group: the surgeon will proceed with pre-incisional infiltration with lidocaine and adrenaline at the intraoral and intranasal submucosal level in the maxilla to block the terminal branches of the maxillary nerve.
- Study Group: the anesthesiologist will proceed to the bilateral blockade of the maxillary nerve echoguided by suprazigomatic route with ropivacaine and dexmedetomidine; and the surgeon will infiltrate with intraoral and intranasal submucosal adrenaline in the maxilla.

PHARMACOLOGICAL TREATMENTS

- Control group: Infiltration performed by the surgeon at the intraoral and intranasal submucosal level in the maxilla (blockage of terminal branches of the maxillary nerve) after intubation and previous to surgical incision.

A total of 50ml of the following preincisional mixture is infiltrated: ½ amp Adrenaline + 1amp Lidocaine 2% in physiological saline (SF) 100ml.

- Study group: Bilateral ultrasound-guided maxillary nerve block by suprazigomatic route after intubation and previous to surgical incision performed by the anesthesiologist.

A total of 5ml of Ropivacaine 0.37% infiltrated on each side.

Together with adrenaline infiltration performed by the surgeon at the intraoral and intranasal submucosal level in the maxilla.

A total of 50ml of the following preincisional mixture is infiltrated: ½ amp Adrenaline + 110ml SF.

Previous to the surgical incision, fentanyl 0.5mcg/kg/ ev will be administered again to all patients and infusion of target-controlled infusion (TCI) of remifentanyl (RMF) at 2ng / ml effect concentration will be initiated. It will be administered intraoperatively to all patients as adjuvant therapy, as long as there is no contraindication, corticotherapy (methylprednisolone 15mg / kg / ev), antifibrinolytic agent (tranexamic acid 15mg / kg / ev), gastric protection (ranitidine 50mg / ev), antiemetic agent (ondansetron 4mg / ev) and analgesics (paracetamol 1g / ev, dexketoprofen 50mg / ev, diclofenac 75mg / im) and ketamine in subanesthetic doses (ketamine 20mg / ev in the induction and ketamine 40mg / ev slow intraoperative administration). The mechanical ventilation by controlled volume (6ml / kg) will be adjusted to maintain a CO₂ at the end of expiration around 32-38mmHg. In the intraoperative period, in cases of changes in basal NIBP equal to or greater than 20%, remifentanyl will be increased / reduced in TCI 0.2mcg / ml. If NIBP increases last longer than 5 minutes, administration of remifentanyl bolus 2mcg / ev will proceed. If abrupt drops of the NIBP will proceed to stop the TCI RMF. Patients will be extubated in the operating room after removal of pharyngeal tamponade, gastric aspiration and reversal of neuromuscular relaxation and recovery of protective airway reflexes. In the postoperative period, an EVA value greater than 3 will be considered as insufficient pain control and rescue analgesia will be administered (first anti-inflammatory metamizole 2g / ev, and second opioid methadone 2mg / 15 ' / ev in resuscitation, up to a total of 10mg / ev in the 2h stay in resuscitation, and methadone 5mg / 6h / sc in hospital ward 2-18h post-operative).

Definition of the variables

- demographic data: age (years), sex (man / woman)
- anthropometric data: weight (kg), height (cm)
- comorbidities: free text
- ASA: 1-3

- Temporary structure of evaluations:
 - Post-operative pain measured with the Analog Visual Scale (EVA 0-10): at 2, 4, 8 and 18 h postoperatively.
 - Total intraoperative opioid dose (TCI-RMF effect concentration).
 - Total intravenous dose of opioids-methadone in the postoperative period (mg) in resuscitation (2 hours postoperatively) and subcutaneous methadone in hospitalization (2-18h postoperative).
 - Total dose of rescue analgesics in the postoperative period (mg of intravenous Metamizol) immediately after resuscitation (2 hours postoperatively) and in the hospital ward (2-18h postoperative).
 - Presence of PONV at 2, 4, 8 and up to 18 h postoperatively.
- Time from the departure of the operating room to the beginning of tolerance orally (hours)
- Complications derived from the administration of LA
- Complications derived from infiltration with lidocaine and adrenaline
- Complications derived from the bilateral blockade of the maxillary nerve echoguided by suprazigomatic route with ropivacaine

CALCULATION OF THE SAMPLE AND STATISTICAL ANALYSIS

The method of sample selection provides for the random assignment of patients in two groups:

1. Surgical pre-incision infiltration of LA lidocaine-adrenaline at submucosal level to block the terminal branches of the maxillary nerve practiced by the surgeon.
2. Surgical pre-incision bilateral maxillary nerve blockade ultrasound guided by suprazigomatic route practiced by the anesthesiologist.

The analgesic effectiveness of the blocks is evaluated by the consumption of methadone in the first 2 post-operative hours. This measure will be considered the primary response from which to estimate the necessary sample size.

The sample size will directly depend on the clinically relevant minimum difference between the average level of methadone consumption at 2h of both groups.

The article by Moro concludes a similar effect of morphine and methadone in the control of post-operative pain, so that the data reported in studies using morphine will be extrapolated to the use of methadone. At least, the data for morphine will be considered a lower level, given the great interpersonal variability of the drugs.

The author Kitlik reports postoperative consumptions of bolus morphine of 7.5 ± 4.0 in a group of patients with Transabdominal Plane-TAP block in abdominal surgery (figure 2, page 106). This deviation will be the one used in the sample size calculations. No randomized clinical trials similar to ours have been found in adults.

The following sample sizes for of minimum

Table 1.- Total needed to mean level of consumption and

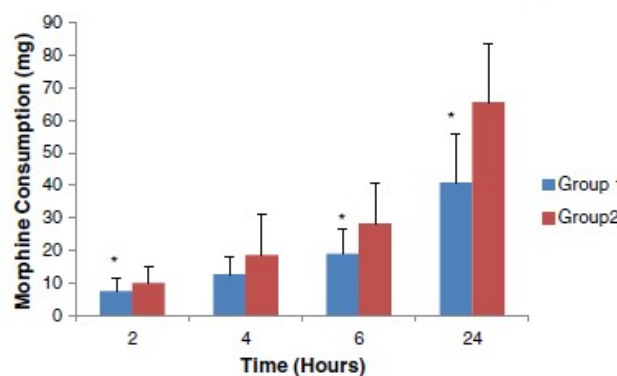


Fig. 2. Postoperative morphine requirements in each group. * Indicates significantly lower morphine requirement Group 1 (n = 25) compared to Group 2 (n = 25). (P < 0.05). Values are mean (SD).

table shows different values difference:

sample size differentiate the methadone statistical

power, assuming a standard deviation of ± 4 in the groups for a confidence level of 95% and a t test of independent samples.

Minimum difference to be detected in the average consumption (mg)	Size effect (d)	Power reached		
		70%	80%	90%
1 (+10%)	0,2 (small)	398	506	676
2 (+25%)	0,5 (medium)	102	128	172
3 (+33%)	0,8 (large)	46	58	78
4 (+44%)	1,0 (extra large)	28	34	46

For example, suppose an average level of methadone consumption at 2 h is 9 and 12 mg in both groups, that is, a difference of 3 mg, or what is the same, 33% in relative terms. This percentage difference can be considered clinically relevant and is equivalent to an effect size $d = 0.8$ (large). If for the researchers these 3 mg difference in consumption is already relevant, a total of 58 patients (29 per group) are needed to detect the difference as significant with a power of 80%.

Depending on the minimum clinically relevant difference that you wish to detect, the sample size may vary according to the figures provided in the table above.

Note also in Figure 2 of the Kitlik article that at 24h the average consumption is 40 ± 15 mg in the TAP group. Therefore, a difference of + 25% with another group (average 50 mg) would imply a medium-large effect size (and not medium, as now).

That means, if the total consumption during the first 24 hours is taken as a response variable, the necessary sample sizes will tend to be smaller.

Concerning the future statistical methodology to be used, it is also expected to use a nonparametric Brunner-Langer model for longitudinal data (equivalent to the classic ANOVA), in order to compare the groups in terms of the general evolution pattern. This model contrasts the hypothesis of homogeneity of the evolution of the degree of pain, and not only the comparison in a specific time-point.

LIMITATIONS

The use of AL with vasoconstrictor (Adrenaline) in the pre-incisional infiltrations practiced by the surgeon provides the following advantages: it prolongs the duration of anesthesia, decreases the systemic toxicity by decreasing the proportion of AL that is absorbed into the bloodstream, it increases the intensity of blockade by direct alpha agonist effects in the antinociceptive neurons of the spinal cord, provides local vasoconstriction and decreases bleeding in the surgical field and assists us in the detection of accidental intravascular injection. Therefore, we propose in the study group to continue asking the surgeon to perform the adrenaline infiltrations in the same places where he performs the peripheral blockade of the maxillary nerve to provide vasoconstriction and dissection of the necessary surgical field.

Regarding a bimaxillary osteotomy surgery, the nerves involved are both the maxillary nerve and the mandibular nerve. The maxillary nerve we have already mentioned as we are going to block it in an echoguided way at the level of the pterygopalatine fossa before the exit of its terminal branches, except for the middle meningeal nerve. In the case of the mandibular nerve or inferior maxillary nerve; for its block, we will continue asking the surgeon to perform the pre-incisional infiltration with AL lidocaine. The blocking of the mandibular nerve is not proposed at a more proximal level and in an echoguided manner because with the truncal anesthesia of the mandibular nerve with intraoral access, the results are satisfactory[xxxx].

Ethics

All information is provided to the patient before making the decision to participate or not in the study.

The information is based on the elements included in the guidelines of the Declaration of Helsinki and GCP ICH Guides.

The investigator will describe to the patient all the measures that will be carried out for data protection and patient privacy according with the Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. "It is the adaptation to the Spanish legal system of Regulation (EU) 2016/679 of the European Parliament and the Council of April 27 of 2016.

The investigator must explain to the patient the limitations and risks of the study and the possibility of interrupting their participation in any of the stages of the study without affecting the relationship with the researcher and / or health personnel.

The information sheet and informed consent will be provided to the patient along with a verbal explanation. The patient must accept and sign before initiating any procedure related to the study.

EXPECTED RESULTS

Infiltration with LA in the terminal branches of the maxillary nerve is the common practice for bimaxillary osteotomy surgery, along with the administration of intravenous opioids for the control of perioperative pain. All this has been seen to increase nausea and vomiting, resulting in greater dissatisfaction on the part of the patient and longer hospital stay. On the other hand, with the bilateral ultrasound blockade at the suprazigomatic level in a safe and ultrasound-guided manner, with adjusted doses of ropivacaine, it is expected to decrease the doses of opioids in the perioperative period; and therefore, increase patient safety and satisfaction, through greater pain control and decreased PONV; as well as, accelerate tolerance orally in the postoperative period and hospital discharge

The choice of LA reflects the balance between the rapidity of the onset of action and the desire for a prolonged duration of postoperative analgesia. Since maxillofacial procedures produce significant postoperative pain, the use of long-acting LA will be a recommendation.

The combined solutions of LA have the disadvantage of a short duration of action compared to the isolated use of a long-acting LA. In our study we propose the administration of ropivacaine, in such a way that we obtain a dense sensory block of up to 6-18h in the postoperative period that will benefit the patient in global terms, with less postoperative pain and greater patient comfort. , with a decrease in postoperative nausea and vomiting, initiation of oral tolerance progressively faster and hospital discharge earlier, with lower costs and greater effectiveness for the hospital entity as a whole.

BIBLIOGRAPHY

1. Brković B, Andrić M, Čalasan D, Milić M, Stepić J, Vučetić M, Brajković D, Todorović L. Efficacy and safety of 1% ropivacaine for postoperative analgesia after lower third molar surgery: a prospective, randomized, double-blinded clinical study. Clin Oral Investig 2017;21(3):779-785.
2. Budharapu A, Sinha R, Uppada UK, Subramanya Kumar AV. Ropivacaine: a new local anaesthetic agent in maxillofacial surgery. Br J Oral Maxillofac Surg 2015;53(5):451-4.
3. Cuvillon P, Nouvellon E, Ripart J, Boyer JC, Dehour L, Mahamat A, L'hermite J, Boisson C, Vialles N, Lefrant JY, de La Coussaye JE. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesth Analg 2009;108(2):641-9.
4. Mesnil M, Dadure C, Captier G, Raux O, Rochette A, Canaud N, Sauter M, Capdevila X. A new approach for peri-operative analgesia of cleft palate repair in infants: the bilateral

suprazigomatic maxillary nerve block. *Pediatric Anesthesia* 2010;20:343-349.

5. Sola C, Raux O, Savath L, Macq C, Capdevila X, Dadure C. Ultrasound guidance characteristics and efficiency of suprazigomatic maxillary nerve blocks in infants: a descriptive prospective study. *Pediatric Anesthesia* 2012;22:841-846.
6. Chiono J, Raux O, Bringuier S, Pharm D, Sola C, Bigorre M, Capdevila X, Dadure C. Bilateral Suprazygomatic Maxillary Nerve Block for Cleft Palate Repair in Children. *Anesthesiology* 2014;120:1362-9.
7. Bouzinac A, Tournier J-J, Delbos A. Ultrasound-guided maxillary nerve block in adults: feasibility and efficiency for postoperative analgesia after maxillary osteotomy. *Minerva Anest* 2014;80(7):860-1.
8. Sisk AL. Vasoconstrictors in local anesthesia for dentistry. *Anesth Prog* 1992;39(6):187-93.
9. El-Boghdady K, Brull R, Shembi H, Abdallah FW. Perineural Dexmedetomidine is more effective than Clonidine when added to local anesthetic for Supraclavicular Brachial Plexus Block: A Systematic Review and Meta-analysis. *Anesth Analg* 2017;124:2008-20.
10. Moro ET, Lambert MF, Pereira AL, Arthioli T, Graicer G, Bevilacqua J, Bloomstone J. The effect of methadone on postoperative quality of recovery in patients undergoing laparoscopic cholecystectomy: A prospective, randomized, double blinded, controlled clinical trial. *Journal of Clinical Anesthesia* 53 (2019) 64–69. <https://doi.org/10.1016/j.jclinane.2018.09.031>
11. Kitlik A, Erdogan MA, Ozgul U, Aydogan MS, Ucar M, Toprak HI, Colak C, Durmus M. Ultrasound-guided transversus abdominis plane block for postoperative analgesia in living liver donors: A prospective, randomized, double-blinded clinical trial. *Journal of Clinical Anesthesia* 37 (2017) 103–107. <http://dx.doi.org/10.1016/j.jclinane.2016.12.018>